Use of intravenous methylene blue for the treatment of refractory hypotension after cardiopulmonary bypass

To the Editor:

We read with great interest the article by Yiu, Robin, and Pattison[1] titled "Reversal of Refractory Hypotension With Single-Dose Methylene Blue After Coronary Bypass Surgery." The authors reported the successful reversal of post–cardiopulmonary bypass (CPB) vasoplegia (defined as systolic blood pressure < 90 mm Hg associated with low systemic vascular resistance) with the use of a single dose (2 mg/kg) of intravenous methylene blue, achieving hemodynamic stability and rapid weaning (1 hour) from high-dose vasoconstrictor (norepinephrine) support.

We recently used methylene blue in the treatment of a patient with both severe low cardiac output and refractory vasoplegia resulting from a post-CPB severe inflammatory response. Like Yiu, Robin, and Pattison, we noted rapid restoration of peripheral vascular tone, allowing us to discontinue the high-dose norepinephrine drip by the time the infusion dose was completed.

The patient was a 20-year-old man undergoing aortic valve replacement for severe aortic stenosis with severe left ventricular dysfunction and moderate pulmonary hypertension. Fourteen years earlier he had had aggressive radiation therapy and chemotherapy for Hodgkin lymphoma, and he had been on a program of furosemide, digoxin, and enalapril. The operation was conducted under moderate hypothermia (28°C) with antegrade/retrograde cold blood cardioplegia. Operative findings revealed a small, fibrotic, heavily calcified aortic anulus and low-placed stenotic coronary ostia. After extensive debridement and annular enlargement (Manouguian type), a No. 19 St Jude Medical mechanical valve (St Jude Medical, Inc, St Paul, Minn) was implanted and a vein graft was placed to the left anterior descending coronary artery. The patient could not be weaned from CPB despite high-dose inotropic and vasoconstrictor support, resulting in placement of biventricular mechanical assist devices (Thoratec; Thoratec Laboratories, Pleasanton, Calif). The postoperative course at 48 hours showed refractory hypotension, marginal cardiac output, and high pulmonary artery pressures despite the use of high doses of epinephrine, norepinephrine, dobutamine, milrinone, and inhaled nitric oxide. The infusion of 1% methylene blue, 2 mg/kg, over 30 minutes and a second dose given 22 hours later produced the hemodynamic changes listed in Table I.

The mechanism of systemic inflammatory response syndrome after CPB is not completely understood and seems to be multifactorial. At least part of the inflammatory response is a consequence of substantial nitric oxide release at the endothelial level, accounting for the persistent capillary relaxation and low systemic vascular resistance.[2,3] The methylene blue inhibits the guanylate cyclase enzyme, blunting the release of nitric oxide and therefore promoting an increase in the peripheral vascular tone. Andrade and associates[4] reported the successful use of methylene blue to control the inflammatory response after cardiac operations and in patients with anaphylactic shock, although those patients had a more distinct vasodilatory shock with increased cardiac output and index. Methylene blue is used clinically for the treatment of methemoglobinemia and the rare cases of nitroprusside toxicity. Few significant secondary effects are described and include cardiac arrhythmias and coronary vasoconstriction with angina. As in the report by Evora, Roselino, and Schiaveto,[5] our patient had a transient nodal rhythm (5 minutes) and ventricular ectopy that disappeared after the infusion rate was slowed. Also, different from that report, we used a 1% concentration instead of the 4% described.

Our patient had a mixed disorder with predominant biventricular dysfunction and the inflammatory response resulting from 11 hours of CPB. The infusion of methylene blue allowed rapid (30 minutes) discontinuation of norepinephrine and a substantial decrease in the epinephrine requirement for pressure support. Unfortunately, despite the initial hemodynamic improvement, multiple system organ failure progressively developed and the patient died on postoperative day 10.

We believe methylene blue may be of value as an addition-

Table I. *Hemodynamic changes*

Time	*BP (mean)*	*HR*	*SVR*	*CVP*	*CI*	*PAP (mean)*	*NE*	*E*	*DB*	*MN*	*NO*
Dose α	80/51 (62)	130	538	28	3.0	42/23 (29)	0.2	0.3	5	0.75	50
1 hour	118/59 (80)	110	842	22	1.6	41/24 (29)	—	0.1	5	0.50	50
2 hour	98/57 (67)	112	800	22	1.6	41/24 (29)	—	0.1	5	0.75	40
3 hour	100/42 (61)	108	996	18	2.0	37/23 (28)	—	0.05	5	0.75	40
6 hour	93/44 (60)	84	690	23	2.4	42/24 (29)	—	0.15	5	0.75	30
Dose κ	83/45 (59)	109	586	24	2.6	44/29 (33)	—	0.15	7.5	0.75	20
1 hour	116/62 (81)	115	1058	24	2.6	51/30 (36)	—	0.15	0.5	0.50	20
4 hour	117/59 (81)	114	991	26	2.4	47/28 (33)	—	0.15	0.5	0.50	—

Dose α, 2 mg/kg dose; *BP*, blood pressure (mm Hg); *SVR*, systemic vascular resistance (dynes · sec^{-1} · cm^{-5}); *CVP*, central venous pressure (mm Hg); *CI*, cardiac index (L · min^{-1} · m^{-2}; *PAP*, pulmonary artery pressure (mm Hg); *NE*, norepinephrine (μg · kg^{-1} · min^{-1}); *E*, epinephrine (μg · kg^{-1} · min^{-1}); *DB*, dobutamine (mg · kg^{-1} · min^{-1}); *MN*, milrinone (mg · kg^{-1} · min^{-1}); *NO*, nitric oxide (ppm: particles per million); κ, second dose 72 hours postoperatively (1 mg/kg).

al drug for the treatment of patients with refractory vasoplegia after CPB. Further research, of course, is needed.

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Notes about axillary cannulation

To the Editor:

We read with interest the comments[1,2] on our article about axillary cannulation for type A aortic dissection,[3] and we are honored by the attention paid to our work.

Since August 1998, axillary cannulation has been used in 13 more patients with type A aortic dissection in our institution. The axilla has now become our site of choice for arterial perfusion. No brachial plexus injury has been recorded and no lesion of the axillary artery has occurred. These results emphasize that direct cannulation is safe when a lateral approach is used, as well. Moreover, in the past 5 years, we have performed this lateral vascular access in more than 130 axillo-femoral bypass procedures for peripheral disease without local complications.

We fully agree that the graft interposition technique offers important advantages in terms of systemic pressure monitoring and decannulation. However, direct cannulation is more expeditious, an advantage in patients with type A aortic dissection. Furthermore, it is more difficult to evacuate air from the graft than from the cannula, and this may be disadvantageous.

Another point of controversy is that the choice of the left axillary artery, instead of the right, precludes the use of this route for elective cerebral protection. Besides our shared apprehension about manipulating the innominate artery, another major concern remains that of embolization at the beginning of perfusion, which can be avoided if the left axillary artery is used.

To assess this point, we have performed transcranial Doppler monitoring of the bilateral middle cerebral arteries in 6 patients treated for acute type A aortic dissection. Three of them received right axillary cannulation and 3 left axillary cannulation. Although none of the patients had clinically detectable consequences, microembolic signals were detected at the beginning of the perfusion in all patients having right axillary cannulation, whereas no signal was detected in the 3 patients with left axillary cannulation.

We have encountered only one difficulty with axillary artery cannulation that does not occur with femoral artery cannulation. During total aortic arch replacement for type A aortic dissection, at the moment of circulatory arrest, the descending aorta tends to empty. We cannot fill the aorta and the graft retrogradely, as we can with femoral artery cannulation. Therefore, once the anastomosis of the button containing the supra-aortic branches has been completed, we have too much air to evacuate. From this viewpoint, we agree that right axillary artery cannulation provides a theoretical advantage over left axillary artery cannulation by allowing retrograde washing of air bubbles through the common carotid, innominate, and even left subclavian arteries through the vertebral-basilar system.

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Is neck or chest anastomosis preferable during esophageal resection?

To the Editor:

We read with great interest the article by Johansson and associates titled "Pharyngeal Reflux After Gastric Pull-up Esophagectomy With Neck and Chest Anastomoses."[1] This topic is important, controversial, and difficult to study, and the authors are to be commended for addressing it.

The study design is flawed. It is not clear whether the groups are similar in tumor stage, demographics, and other variables that could influence pharyngeal reflux. The type and complexity of the resections are not specified. Reconstructions are atypical and variable. No gastric drainage procedures were performed; thus the occurrence of gastric retention, reflux, and reflux-related complications